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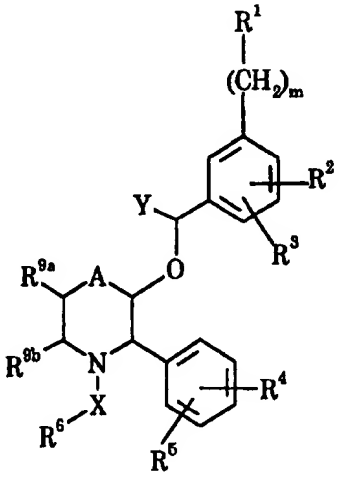
(54) Title: PIPERIDINE AND MORPHOLINE DERIVATIVES AND THEIR USE AS THERAPEUTIC AGENTS

(57) Abstract

The present invention provides compounds of formula (I), wherein R^1 is a 5- or 6-membered aromatic heterocyclic group containing 1, 2, 3 or 4 heteroatoms selected from nitrogen, oxygen and sulphur, which group is optionally substituted; R^2 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, CF_3, OCF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substitued by C_{1-4}alkoxy, where R^a and R^b each independently represent hydrogen or C_{1-4}alkyl; R^3 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or CF_3; R^4, R^5, R^6, R^{9a}, R^{9b}, A, X and Y are as defined in the specification; and m is zero or 1, and pharmaceutically acceptable salts and prodrugs thereof. The compounds are of particular use in the treatment or prevention of pain, inflammation, migraine, emesis and postherpetic neuralgia.



(I)

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PIPERIDINE AND MORPHOLINE DERIVATIVES AND THEIR USE AS THERAPEUTIC AGENTS

This invention relates to a class of aromatic compounds which are useful as tachykinin antagonists. More particularly, the compounds of the invention contain an amine-substituted azo-heterocyclic moiety.

The tachykinins are a group of naturally occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in peripheral nervous and circulatory systems.

The tachykinins are distinguished by a conserved carboxyl-terminal sequence:

Phe-X-Gly-Leu-Met-NH_2

At present, there are three known mammalian tachykinins referred to as substance P, neurokinin A (NKA, substance K, neuromedin L) and neurokinin B (NKB, neuromedin K) (for review see J.E. Maggio, *Peptides* (1985) 6(suppl. 3), 237-242). The current nomenclature designates the three tachykinin receptors mediating the biological actions of substance P, NKA and NKB as the NK_1, NK_2 and NK_3 receptors, respectively.

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including cystitis and bladder detruser hyper-reflexia is reviewed in "Tachykinin Receptors and Tachykinin Receptor Antagonists", C.A. Maggi, R. Patacchini, P. Rovero and A. Giachetti, *J. Auton. Pharmacol.* (1993) 13, 23-93.

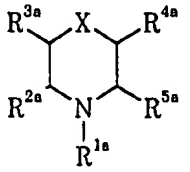
For instance, substance P is believed *inter alia* to be involved in the neurotransmission of pain sensations [Otsuka *et al*, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in *1982 Substance P in the Nervous System*, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" *TIPS* (1987) 8, 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg *et al*, *J. Med Chem*, (1982) 25, 1009) and in arthritis [Levine *et al Science* (1984) 226, 547-549]. Tachykinins have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease [Mantyh *et al Neuroscience* (1988) 25(3), 817-37 and D. Regoli in *"Trends in Cluster Headache"* Ed. Sicuteri *et al* Elsevier Scientific Publishers, Amsterdam (1987) page 85)] and emesis [F. D. Tattersall *et al*, *Eur. J. Pharmacol.*, (1993) 250, R5-R6]. It is also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd *et al* "A Neurogenic Mechanism for Symmetrical Arthritis" in *The Lancet*, 11 November 1989 and Grönblad *et al*, "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in *J. Rheumatol.* (1988) 15(12), 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis, and fibrositis [O'Byrne *et al, Arthritis and Rheumatism* (1990) 33, 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet *et al, Can. J. Pharmacol. Physiol.* (1988) 66, 1361-7], immunoregulation [Lotz *et al, Science* (1988) 241, 1218-21 and Kimball *et al, J. Immunol.* (1988) 141(10), 3564-9] vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh *et al, PNAS* (1988) 85, 3235-9] and, possibly by arresting or slowing ß-amyloid-mediated neurodegenerative changes [Yankner *et al, Science* (1990) 250, 279-82] in senile dementia of the Alzheimer type, Alzheimer's disease and Down's Syndrome.

Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon *et al, Cancer Research* (1992) 52, 4554-7].

Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-Narod *et al*, poster *C.I.N.P. XVIIIth Congress*, 28th June-2nd July 1992], and in disorders of bladder function such as bladder detrusor hyper-reflexia (*Lancet*, 16th May 1992, 1239).

It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosus (European patent specification no. 0 436 334), ophthalmic disease such as conjuctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis (European patent specification no. 0 394 989).

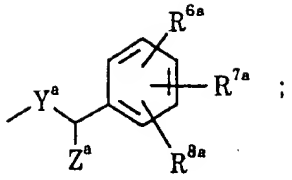
European patent specification no. 0 577 394 (published 5th January 1994) discloses morpholine and thiomorpholine tachykinin receptor antagonists of the general formula



wherein R^{1a} is a large variety of substituents;

R^{2a} and R^{3a} are *inter alia* hydrogen;

R^{4a} is *inter alia*



R^{5a} is *inter alia* optionally substituted phenyl;

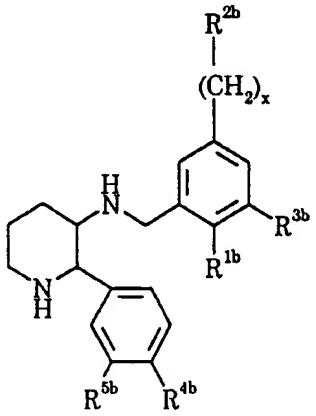
R^{6a}, R^{7a} and R^{8a} are a variety of substituents;

X^a is O, S, SO or SO_2;

Y^a is *inter alia* O; and

Z^a is hydrogen or C_{1-4}alkyl.

International Patent Specification no. WO 95/08549 discloses piperidine derivatives as tachykinin receptor antagonists of the general formula



wherein R^{1b} is C_{1-4}alkoxy;

R^{2b} is optionally substituted tetrazolyl;

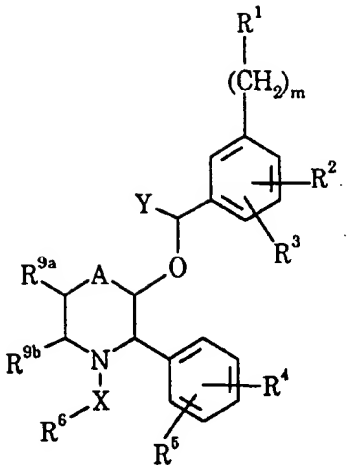
R^{3b} is hydrogen or halogen;

R^{4b} and R^{5b} are hydrogen, halogen, C_{1-4}alkyl, C_{1-4}alkoxy or CF_3; and

x is zero or 1.

We have now found a further class of non-peptides which are potent antagonists of tachykinins, especially of substance P.

The present invention provides compounds of the formula (I):



(I)

wherein

R^1 is a 5- or 6-membered aromatic heterocyclic group containing 1, 2, 3 or 4 heteroatoms selected from nitrogen, oxygen and sulphur, which group is optionally substituted by one or two substituents selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, SR^x, SOR^x, SO_2R^x, phenyl, NR^aR^b, NR^aCOR^x, CH_2COCF_3 and CF_3, where R^a and R^b are independently hydrogen or C_{1-4}alkyl and R^x is C_{1-4}alkyl;

R^2 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, CF_3, OCF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, where R^a and R^b each independently represent hydrogen or C_{1-4}alkyl;

R^3 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or CF_3;

R^4 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, CF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, where R^a and R^b each independently represent hydrogen or C_{1-4}alkyl;

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or CF_3;

R^6 is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O, =S or a C_{1-4}alkyl group, and optionally substituted by a group of the formula ZNR^7R^8 where

Z is C_{1-6}alkylene or C_{3-6}cycloalkylene;

R^7 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-7}cycloalkylC_{1-4}alkyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxyl;

R^8 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-7}cycloalkylC_{1-4}alkyl, or C_{2-4}alkyl substituted by one or two substituents selected from C_{1-4}alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

or R^7, R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy or C_{1-4}alkyl optionally substituted by a C_{1-4}alkoxy or hydroxyl group, and optionally containing a double bond, which ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or $S(O)_2$ or a second nitrogen atom which will be part of a NH or NR^c moiety where R^c is C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy;

or R^7, R^8 and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

or Z, R^7 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

R^{9a} and R^{9b} are each independently hydrogen or C_{1-4}alkyl, or R^{9a} and R^{9b} are joined so, together with the carbon atoms to which they are attached, there is formed a C_{5-7} ring;

A is -O- or $-CH_2-$;

X is an alkylene chain of 1 to 4 carbon atoms optionally substituted by oxo;

Y is hydrogen or a C_{1-4}alkyl group optionally substituted by a hydroxyl group; and

m is zero or 1;

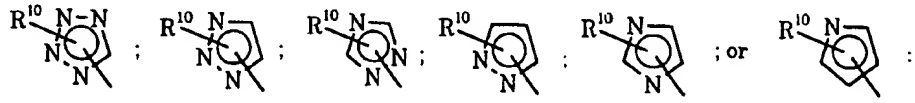
and pharmaceutically acceptable salts and prodrugs thereof.

According to an alternative aspect of the present invention, Y is a C_{1-4}alkyl group optionally substituted by a hydroxyl group.

Certain particularly apt compounds of the present invention include those wherein R^1 is a group selected from pyrrole, furan, thiene, pyridine, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyrazine, pyrimidine, pyridazine, triazole, oxadiazole, thiadiazole, triazine, and tetrazole, each of which heterocyclic groups being optionally substituted as previously defined.

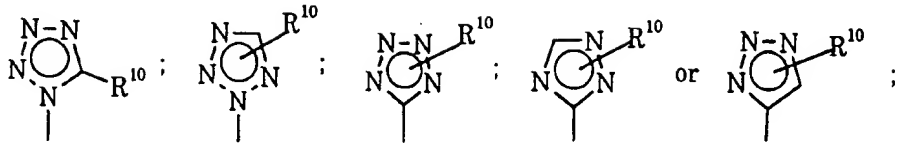
Preferred compounds of the present invention are those wherein R^1 is a group selected from furan, pyridine, pyrazole, imidazole, oxazole, isoxazole, pyrazine, pyrimidine, thiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole and tetrazole, each of which heterocyclic groups being optionally substituted as previously defined.

Certain particularly apt compounds of the present invention include those wherein R^1 is a 5-membered aromatic heterocyclic group. Preferred compounds are those wherein R^1 is a 5-membered aromatic heterocyclic group containing 1, 2, 3 or 4 nitrogen atoms, for instance,



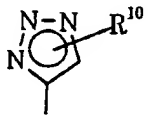
where R^{10} is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, SR^x, SOR^x, SO_2R^x, phenyl, NR^aR^b, NR^aCOR^x, CH_2COCF_3 or CF_3, where R^a and R^b are independently hydrogen or C_{1-4}alkyl, and R^x is C_{1-4}alkyl.

Particularly preferred compounds of the present invention are those wherein R^1 is a group selected from



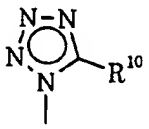
where R^{10} is as previously defined.

An especially preferred class of compound of formula (I) is that wherein R^1 is the group



where R^{10} is as previously defined.

Another especially preferred class of compound of formula (I) is that wherein R^1 is the group



wherein R^{10} is as previously defined.

R^{10} is preferably hydrogen, C_{1-4}alkyl, especially methyl, or CF_3.

Most aptly R^2 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen, CF_3 or OCF_3.

Most aptly R^3 is hydrogen, halogen or CF_3.

Favourably R^2 is hydrogen, C_{1-4}alkoxy, halogen, CF_3 or OCF_3.

Favourably R^3 is hydrogen, fluorine, chlorine or CF_3.

More preferably R^2 is hydrogen, methoxy, ethoxy, propoxy, isopropoxy, fluorine, chlorine, CF_3 or OCF_3.

More preferably R^3 is hydrogen.

Most preferably R^2 is in the meta- or para-position with respect to the group R^1-$(CH_2)_m$-.

Most preferably R^2 is fluorine or CF_3.

Most aptly R^4 is hydrogen.

Most aptly R^5 is hydrogen, fluorine, chlorine or CF_3.

Preferably R^4 is hydrogen and R^5 is hydrogen or 4-fluoro.

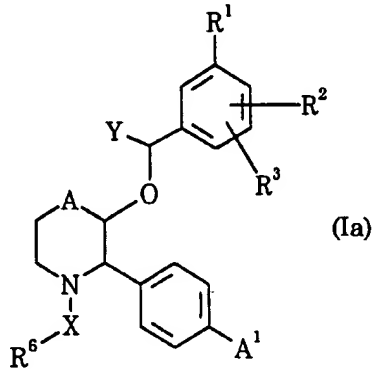
Most aptly R^{9a} and R^{9b} are each independently hydrogen or methyl.

Preferably R^{9a} is hydrogen. Preferably R^{9b} is hydrogen. Most preferably R^{9a} and R^{9b} are both hydrogen.

Preferably m is zero.

Preferably A is -O-.

From the foregoing it will be appreciated that a particularly apt sub-group of compounds of this invention are those of the formula (Ia) and pharmaceutically acceptable salts and prodrugs thereof:



(Ia)

wherein

A, X, Y, R^1, R^2, R^3 and R^6 are as defined in relation to formula (I) and A^1 is fluorine or hydrogen.

According to a second or further aspect of the present invention, a preferred class of compound of formula (I) or (Ia) is that wherein Y represents a C_{1-4}alkyl group; or a pharmaceutically acceptable salt or prodrug thereof.

According to a further or alternative aspect of the present invention, another preferred class of compound of formula (I) or (Ia) is that wherein R^6 is substituted at least by a group of the formula ZNR^7R^8 as defined above; or a pharmaceutically acceptable salt or prodrug thereof.

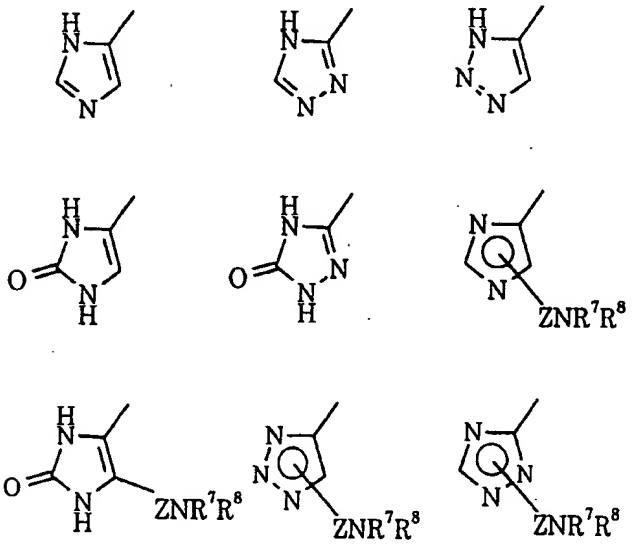
When the group Y in compounds of the formulae (I) or (Ia) is a C_{1-4}alkyl group susbtituted by a hydroxy group,a preferred group is the CH_2OH group.

Another preferred group Y for compounds of the formulae (I) or (Ia) is the CH_3 group.

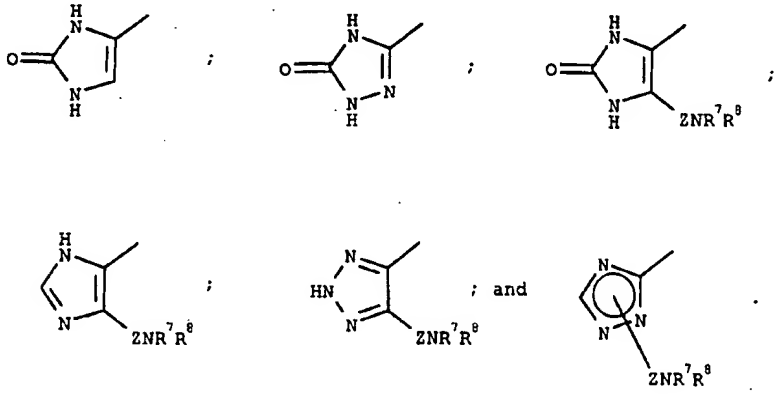
Particularly apt values for X for compounds of the formulae (I) or (Ia) include CH_2, $CH(CH_3)$ and CH_2CH_2 of which the CH_2 group is preferred.

Favourably R^6 is a 5-membered ring.

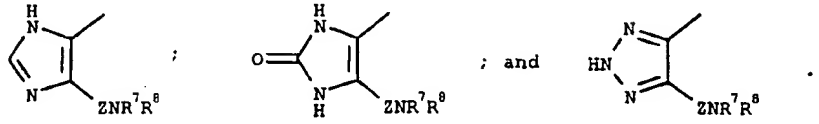
In particular, R^6 may, represent a heterocyclic ring selected from:



Particularly preferred heterocyclic rings represented by R^6 are selected from:

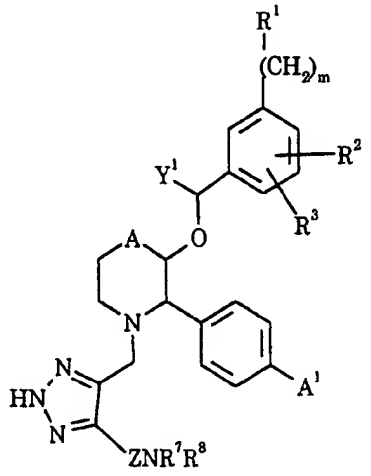


Most especially, R^6 may represent a heterocyclic ring selected from:



A particularly preferred heterocyclic ring represented by R^6 is:

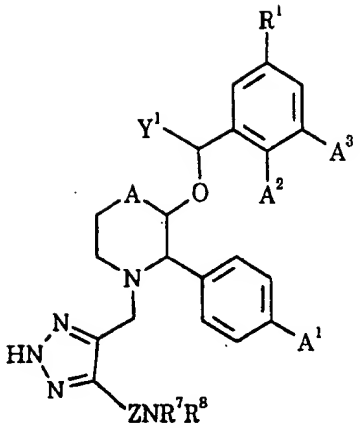
One favoured group of compounds of this invention are of the formula (Ib) and pharmaceutically acceptable salts thereof:



(Ib)

wherein A^1 is as defined in relation to formula (Ia), wherein A, Z, R^1, R^2, R^3, R^7, R^8 and m are as defined in relation to formula (I) and wherein Y^1 is hydrogen or methyl.

A further favoured group of compounds of the present invention are of the formula (Ic) and pharmaceutically acceptable salts thereof:



(Ic)

wherein A^1 is as defined in relation to formula (Ia); Y^1 is hydrogen or methyl; A^2 is hydrogen, C_{1-4}alkoxy, halogen, CF_3 or OCF_3; A^3 is hydrogen, halogen or CF_3; and R^1, R^7, R^8 and Z are as defined in relation to formula (I).

With respect to compounds of the formulae (I), (Ia), (Ib), and (Ic), Z may be a linear, branched or cyclic group. Favourably Z contains 1 to 4 carbon atoms and most favourably 1 or 2 carbon atoms. A particularly favourable group Z is CH_2.

With respect to compounds of the formulae (I), (Ia), (Ib), and (Ic), R^7 may aptly be a C_{1-4}alkyl group or a C_{2-4}alkyl group substituted by a hydroxyl or C_{1-2}alkoxy group, R^8 may aptly be a C_{1-4}alkyl group or a C_{1-4}alkyl group substituted by a hydroxyl or C_{1-2}alkoxy group, or R^7 and R^8 may be linked so that, together with the nitrogen atom to which they are attached, they form an azetidinyl, pyrrolidinyl, piperidyl, morpholino, thiomorpholino, piperazino or piperazino group substituted on the nitrogen atom by a C_{1-4}alkyl group or a C_{2-4}alkyl group substituted by a hydroxy or C_{1-2}alkoxy group.

Where the group NR^7R^8 represents a heteroaliphatic ring of 4 to 7 ring atoms and said ring contains a double bond, a particularly preferred group is 3-pyrroline.

Where the group NR^7R^8 represents a non-aromatic azabicyclic ring system, such a system may contain between 6 and 12, and preferably between 7 and 10, ring atoms. Suitable rings include 5-azabicyclo[2.1.1]hexyl, 5-azabicyclo[2.2.1]heptyl, 6-azabicyclo[3.2.1]octyl, 2-azabicyclo[2.2.2]octyl, 6-azabicyclo[3.2.2]nonyl, 6-azabicyclo[3.3.1]nonyl, 6-azabicyclo[3.2.2]decyl, 7-azabicyclo[4.3.1]decyl, 7-azabicyclo[4.4.1]undecyl and 8-azabicyclo[5.4.1]dodecyl, especially 5-azabicyclo[2.2.1]heptyl and 6-azabicyclo[3.2.1]octyl.

Where R^8 represents a C_{2-4}alkyl group substituted by a 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S, suitable rings include pyrrolidino, piperidino, piperazino, morpholino, or thiomorpholino. Particularly preferred are nitrogen containing heteroaliphatic rings, especially pyrrolidino and morpholino rings.

Particularly suitable moieties ZNR^7R^8 include those wherein Z is CH_2 or CH_2CH_2 and NR^7R^8 is amino, methylamino, dimethylamino, diethylamino, azetidinyl, pyrrolidino and morpholino.

Further preferred moieties represented by ZNR^7R^8 are those wherein Z is CH_2 or CH_2CH_2, R^7 represents hydrogen, C_{1-4}alkyl or C_{3-6}cycloalkyl and R^8 is C_{2-4}alkyl substituted by one or two substituents selected from hydroxy, C_{1-2}alkoxy, azetidinyl, pyrrolidino, piperidino, morpholino or thiomorpholino.

In particular, Z is preferably CH_2 and NR^7R^8 is preferably dimethylamino, azetidinyl or pyrrolidino, especially dimethylamino.

As used herein, the term "alkyl" or "alkoxy" as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

The cycloalkyl groups referred to herein may represent, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. A suitable cycloalkylalkyl group may be, for example, cyclopropylmethyl.

As used herein, the terms "alkenyl" and "alkynyl" as a group or part of a group means that the group is straight or branched. Examples of suitable alkenyl groups include vinyl and allyl. A suitable alkynyl group is propargyl.

When used herein the term halogen means fluorine, chlorine, bromine and iodine. The most apt halogens are fluorine and chlorine of which fluorine is preferred.

Specific compounds within the scope of this invention include:
[2*S*,3*S*]-1-[(5-(dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl)-phenylmethoxy]piperidine;
[2*S*,3*S*]-1-[(5-(dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[3-(5-methyl-1H-tetrazol-1-yl)-5-(trifluoromethyl)-phenylmethoxy]piperidine;
and pharmaceutically acceptable salts or prodrugs thereof.

Further preferred compounds within the scope of the present invention are described in the Examples described herein.

In a further aspect of the present invention, the compounds of formula (I) will preferably be prepared in the form of a pharmaceutically acceptable salt, especially an acid addition salt.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid,

p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

Thus, for example, certain preferred prodrugs may not be antagonists of tachykinin, particularly substance P, activity to any significant extent (or not at all). Such compounds, however, are still advantageous in treating the various conditions described herein, especially where an injectable formulation is preferred.

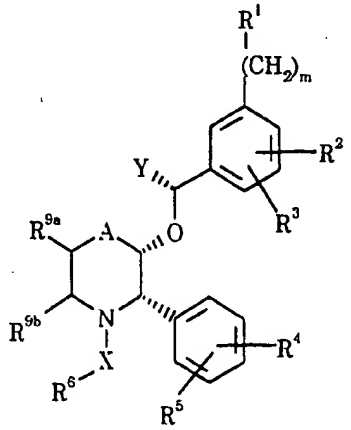
The advantages of a prodrug may lie in its physical properties, such as enhanced water solubility for parenteral administration compared with

the parent drug, or it may enhance absorption from the digestive tract, or it may enhance drug stability for long-term storage. Ideally a prodrug will improve the overall efficacy of a parent drug, for example, through the reduction of toxicity and unwanted effects of drugs by controlling their absorption, blood levels, metabolism, distribution and cellular uptake.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The compounds according to the invention have at least three asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The preferred compounds of the formula (I), (Ia), (Ib) and (Ic), will have the 2- and 3- substituent cis. The preferred stereochemistry at the 2-position is either (R) when A is -O- or (S) when A is $-CH_2-$, for instance, that possessed by the compound of Example 1 (i.e. 2-(S)). The preferred stereochemistry of the 3-position is that possessed by the compound of Example 1 (i.e. 3-(S)). The preferred stereochemistry of the carbon to which the group Y is either (R) when Y is C_{1-4}alkyl (e.g. methyl) or (S) when Y is C_{1-4}alkyl substituted by hydroxy (e.g. CH_2OH). Thus for example as shown in formula (Id)



(Id)

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in association with a pharmaceutically acceptable carrier.

Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Preferred compositions for administration by injection include those comprising a compound of formula (I), as the active ingredient, in association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Suitable surface-active agents include anionic agents such as sodium bis-(2-ethylhexyl)sulfosuccinate (docusate sodium), cationic agents, such as alkyltrimethylammonium bromides, (e.g. cetyltrimethylammonium bromide (cetrimide)), and in particular, non-ionic agents, such as polyoxyethylenesorbitans (e.g. Tween™ 20, 40, 60, 80 or 85) and other sorbitans (e.g. Span™ 20, 40, 60, 80 or 85). Compositions with a surface-active agent will conveniently comprise between 0.05 and 5% surface-active agent, and preferably between 0.1 and 2.5%. It will be appreciated that other ingredients may be added, for example mannitol or other pharmaceutically acceptable vehicles, if necessary.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infonutrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example

glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion will preferably comprise fat droplets between 0.1 and 1.0μm, particularly 0.1 and 0.5μm, and have a pH in the range of 5.5 to 8.0.

Particularly preferred emulsion compositions are those prepared by mixing a compound of formula (I) with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The present invention futher provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity.

Thus, for example, an excess of tachykinin, and in particular substance P, activity is implicated in a variety of disorders of the central nervous system. Such disorders include mood disorders, such as

depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders; schizophrenia and other psychotic disorders, for example, schizophreniform disorders, schizoaffective disorders, delusional disorders, brief psychotic disorders, shared psychotic disorders and psychotic disorders with delusions or hallucinations; delerium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple aetiologies; Parkinson's disease and other extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremour; substance-related disorders arising from the use of alcohol, amphetamines (or amphetamine-like substances) caffeine, cannabis, cocaine, hallucinogens, inhalants and aerosol propellants, nicotine, opioids, phenylglycidine derivatives, sedatives, hypnotics, and anxiolytics, which substance-related disorders include dependence and abuse, intoxication, withdrawal, intoxication delerium, withdrawal delerium, persisting dementia, psychotic disorders, mood disorders, anxiety disorders, sexual dysfunction and sleep disorders; epilepsy; Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, for

example diabetic and chemotherapy-induced neuropathy, and postherpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia and other neuralgias; and cerebral vascular disorders due to acute or chronic cerebrovascular damage such as cerebral infarction, subarachnoid haemorrhage or cerebral oedema.

Tachykinin, and in particular substance P, activity is also involved in nociception and pain. The compounds of the present invention will therefore be of use in the prevention or treatment of diseases and conditions in which pain predominates, including soft tissue and peripheral damage, such as acute trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, myofascial pain syndromes, headache, episiotomy pain, and burns; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, odontalgia, abdominal pain, gynaecological pain, for example, dysmenorrhoea, and labour pain; pain associated with nerve and root damage, such as pain associated with peripheral nerve disorders, for example, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; pain associated with carcinoma, often referred to as cancer pain; central nervous system pain, such as pain due to spinal cord or brain stem damage; low back pain; sciatica; ankylosing spondylitis, gout; and scar pain.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, adult respiratory distress syndrome, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal

conjunctivitis, and the like; ophthalmic conditions associated with cell proliferation such as proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of neoplasms, including breast tumours, neuroganglioblastomas and small cell carcinomas such as small cell lung cancer.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of gastrointestinal (GI) disorders, including inflammatory disorders and diseases of the GI tract such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the neuronal control of viscera, ulcerative colitis, Crohn's disease, irritable bowel syndrome and emesis, including acute, delayed or anticipatory emesis such as emesis induced by chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, for example, motion sickness, vertigo, dizziness and Meniere's disease, surgery, migraine, variations in intercranial pressure, gastro-oesophageal reflux disease, acid indigestion, over indulgence in food or drink, acid stomach, waterbrash or regurgitation, heartburn, for example, episodic, nocturnal or meal-induced heartburn, and dyspepsia.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of a variety of other conditions including stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; plasma extravasation resulting from cytokine chemotherapy, disorders of bladder function such as cystitis, bladder detrusor hyper-reflexia and incontinence; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and

vasospastic diseases such as angina, vascular headache, migraine and Reynaud's disease; and pain or nociception attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

The compounds of formula (I) are also of value in the treatment of a combination of the above conditions, in particular in the treatment of combined post-operative pain and post-operative nausea and vomiting.

The compounds of formula (I) are particularly useful in the treatment of emesis, including acute, delayed or anticipatory emesis, such as emesis induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in intercranial pressure. Most especially, the compounds of formula (I) are of use in the treatment of emesis induced by antineoplastic (cytotoxic) agents including those routinely used in cancer chemotherapy.

Examples of such chemotherapeutic agents include alkylating agents, for example, nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action such as nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example, folic acid, purine or pyrimidine antagonists; mitotic inhibitors, for example, vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic antibiotics.

Particular examples of chemotherapeutic agents are described, for instance, by D. J. Stewart in *Nausea and Vomiting: Recent Research and Clinical Advances*, Eds. J. Kucharczyk *et al*, CRC Press Inc., Boca Raton, Florida, USA (1991) pages 177-203, especially page 188. Commonly used chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin

and chlorambucil [R. J. Gralla *et al* in *Cancer Treatment Reports* (1984) 68(1), 163-172].

The compounds of formula (I) are also of use in the treatment of emesis induced by radiation including radiation therapy such as in the treatment of cancer, or radiation sickness; and in the treatment of post-operative nausea and vomiting.

It will be appreciated that the compounds of formula (I) may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or sequential use for the relief of emesis. Such combined preparations may be, for example, in the form of a twin pack.

A further aspect of the present invention comprises the compounds of formula (I) in combination with a 5-HT_3 antagonist, such as ondansetron, granisetron or tropisetron, or other anti-emetic medicaments, for example, a dopamine antagonist such as metoclopramide. Additionally, a compound of formula (I) may be administered in combination with an anti-inflammatory corticosteroid, such as dexamethasone. Furthermore, a compound of formula (I) may be administered in combination with a chemotherapeutic agent such as an alkylating agent, antimetabolite, mitotic inhibitor or cytotoxic antibiotic, as described above. In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

When tested in the ferret model of cisplatin-induced emesis described by F. D. Tattersall *et al*, in *Eur. J. pharmacol.*, (1993) 250, R5-R6, the compounds of the present invention were found to attenuate the retching and vomiting induced by cisplatin.

The compounds of formula (I) are also particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis and headache,

including migraine, acute or chronic tension headache, cluster headache, temporomandibular pain, and maxillary sinus pain.

The present invention further provides a compound of formula (I) for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

For the treatment of certain conditions it may be desirable to employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a bronchodilator, such as a β_2-adrenergic receptor agonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

Likewise, a compound of the present invention may be employed with a leukotriene antagonists, such as a leukotriene D_4 antagonist such as a compound selected from those disclosed in European patent specification nos. 0 480 717 and 0 604 114 and in US patent nos. 4,859,692 and 5,270,324. This combination is particularly useful in the treatment of respiratory diseases such as asthma, chronic bronchitis and cough.

The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective

amount of a compound of formula (I) and an effective amount of a bronchodilator.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

It will be appreciated that for the treatment or prevention of migraine, a compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or 5-HT_1 agonists, especially sumatriptan.

Likewise, for the treatment of behavioural hyperalgesia, a compound of the present invention may be used in conjunction with an antagonist of N-methyl D-aspartate (NMDA), such as dizocilpine.

For the treatment or prevention of inflammatory conditions in the lower urinary tract, especially cystitis, a compound of the present invention may be used in conjunction with an anti-inflammatory agent such as a bradykinin receptor antagonist.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

It will be appreciated that for the treatment or prevention of pain or nociception, a compound of the present invention may be used in conjunction with other analgesics, such as acetaminophen (paracetamol), aspirin and other NSAIDs and, in particular, opioid analgesics, especially morphine. Specific anti-inflammatory agents include diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam and sulindac. Suitable opioid analgesics of use in conjunction with a compound of the present invention include morphine, codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and pentazocine; or a pharmaceutically acceptable salt thereof. Preferred salts

of these opioid analgesics include morphine sulphate, morphine hydrochloride, morphine tartrate, codeine phosphate, codeine sulphate, dihydrocodeine bitartrate, diacetylmorphine hydrochloride, hydrocodone bitartrate, hydromorphone hydrochloride, levorphanol tartrate, oxymorphone hydrochloride, alfentanil hydrochloride, buprenorphine hydrochloride, butorphanol tartrate, fentanyl citrate, meperidine hydrochloride, methadone hydrochloride, nalbuphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate (2-naphthalenesulphonic acid (1:1) monohydrate), and pentazocine hydrochloride.

Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and an analgesic, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and an analgesic as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of pain or nociception.

The excellent pharmacological profile of the compounds of the present invention offers the opportunity for their use in therapy at low doses thereby minimising the risk of unwanted side effects.

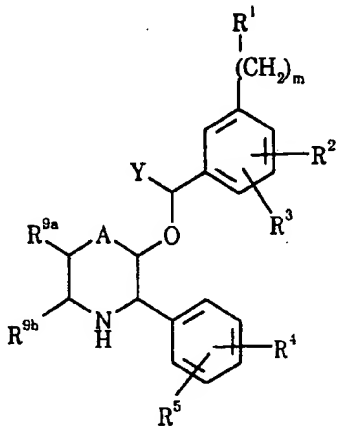
In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of emesis using an injectable formulation, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 1 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

According to a general process (A), the compounds according to the invention may be prepared from compounds of formula (II)



(II)

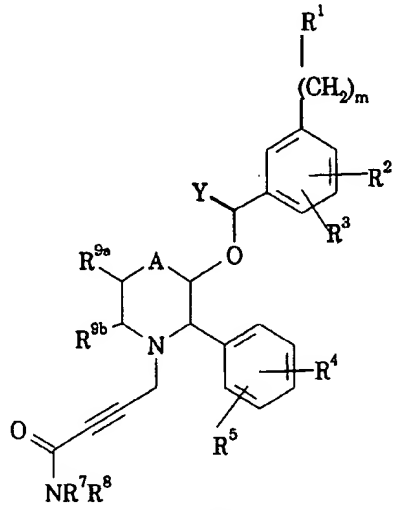
wherein R^1, R^2, R^3, R^4, R^5, R^{9a}, R^{9b}, A, Y and m are as defined in relation to formula (I) by reaction with a compound of formula (III):

$$X^1\text{-}X\text{-}R^{6a} \qquad \text{(III)}$$

where X is as defined in relation to formula (I), R^{6a} is a group of the formula R^6 as defined in relation to formula (I) or a precursor therefor and X^1 is a leaving group such as bromine or chlorine; and, if R^{6a} is a precursor group, converting it to a group R^6 (in which process any reactive group may be protected and thereafter deprotected if desired).

This reaction may be performed in conventional manner, for example in an organic solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate.

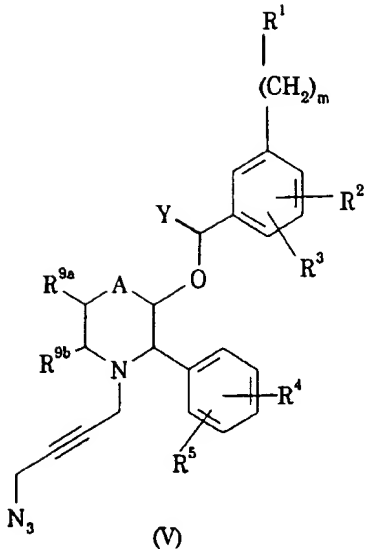
According to another process (B), compounds of formula (I) wherein R^6 represents 1,2,3-triazol-4-yl substituted by $CH_2NR^7R^8$, and X is $-CH_2-$, may be prepared by reaction of a compound of formula (IV)



(IV)

with an azide, for example, sodium azide in a suitable solvent such as dimethylsulphoxide at a temperature of between 40°C and 100°C, followed by reduction of the carbonyl group adjacent to $-NR^7R^8$ using a suitable reducing agent such as lithium aluminium hydride at at a temperature between -10°C and room temperature, conveniently at room temperature.

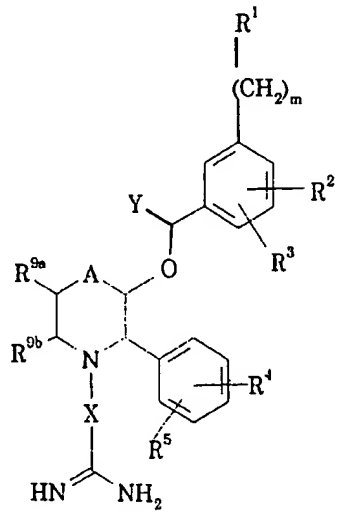
Alternatively, according to a process (C), compounds of formula (I) wherein R^6 represents 1,2,3-triazol-4-yl substituted by CH2NR7R8, and X is $-CH_2-$, may be prepared by reaction of a compound of formula (V)



(V)

with an amine of formula NHR^7R^8, in a suitable solvent such as an ether, for example, dioxan, at elevated temperature, for example, between 50°C and 100°C, in a sealed tube, or the like. This reaction is based upon that described in *Chemische Berichte* (1989) 122, p. 1963.

According to another process, (D), compounds of formula (I) wherein R^6 represents substituted or unsubstituted 1,3,5-triazine may be prepared by reaction of intermediates of formula (VI):

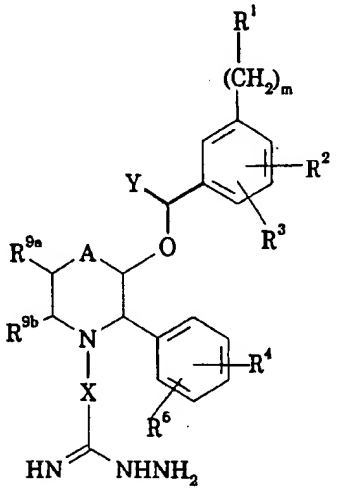


(VI)

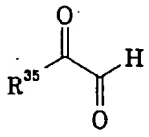
with substituted or unsubstituted 1,3,5-triazine.

The reaction is conveniently effected in a suitable organic solvent, such as acetonitrile, at elevated temperature, such as 80-90°C, preferably about 82°C.

According to a further process, (E), compounds of formula (I) wherein R^6 represents substituted or unsubstituted 1,2,4-triazine may be prepared by reaction of an intermediate of formula (VII) with a dicarbonyl compound of formula (VIII):



(VII)

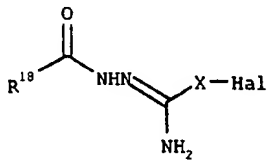


(VIII)

wherein R^{35} represents H or a suitable substituent such as ZNR^7R^8.

The reaction is conveniently effected in a suitable organic solvent, such as an ether, e.g. tetrahydrofuran, conveniently at ambient temperature.

According to a further process (F), compounds of formula (I) wherein R^6 represents a substituted 1,2,4-triazolyl group may be prepared by reaction of an intermediate of formula (II) with a compound of formula (IX)



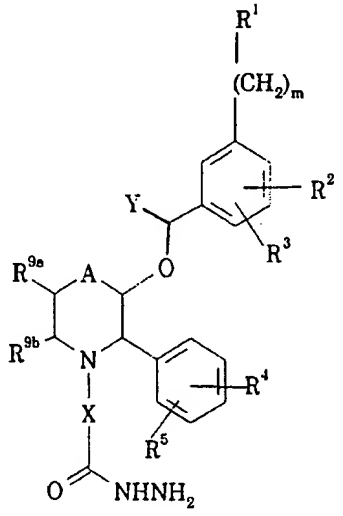
(IX)

wherein X is as defined in relation to formula (I), Hal is a halogen atom, for example, bromine, chlorine or iodine and R^{18} is H, $CONH_2$ or OCH_3 (which is converted to an oxo substituent under the reaction conditions), in the presence of a base, followed where necessary by conversion to a compound of formula (I), for example, by reduction of the $CONH_2$ group to CH_2NH_2.

Suitable bases of use in the reaction include alkali metal carbonates such as, for example, potassium carbonate. The reaction is conveniently effected in an anhydrous organic solvent such as, for example, anhydrous dimethylformamide, preferably at elevated temperature, such as about 140°C.

A suitable reducing agent for the group $CONH_2$ is lithium aluminium hydride, used at between -10°C and room temperature.

According to another process, (G), compounds of formula (I) wherein R^6 represents thioxotriazolyl may be prepared from intermediates of formula (X)



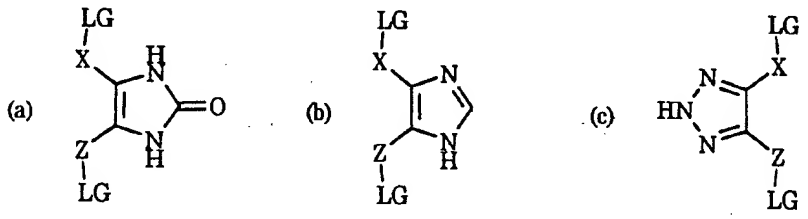
(X)

by reaction with a compound of formula HNCS, in the presence of a base.

Suitable bases of use in the reaction include organic bases such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction is

conveniently effected in a suitable organic solvent, such as alcohol, e.g. butanol.

According to a further alternative general process (H), compounds of formula (I) wherein the heterocycle R^6 is substituted by ZNR^7R^8, may be prepared from an intermediate of formula (II) as defined above with one of the compounds of formula (XI):



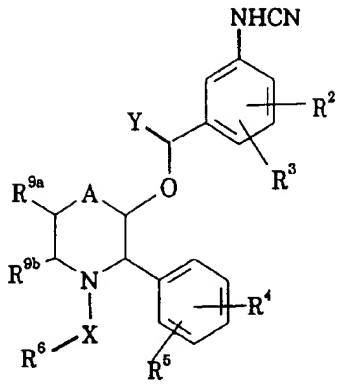
(XI)

wherein each LG, which may be the same or different, is a leaving group, such as an alkyl- or arylsulphonyloxy group (e.g. mesylate or tosylate) or, in particular, a halogen atom, (e.g. bromine, chlorine or iodine) and X and Z are as defined in formula (I), followed by reaction of the resultant compound with an amine NHR^7R^8 to complete the ZNR^7R^8 moiety.

This reaction is conveniently effected in an organic solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate.

It will be appreciated that, where necessary, reactive groups may be protected, thus for example, the NH groups of an imidazolinone of formula (XIa) may be protected by any suitable amine protecting group such as an acetyl group.

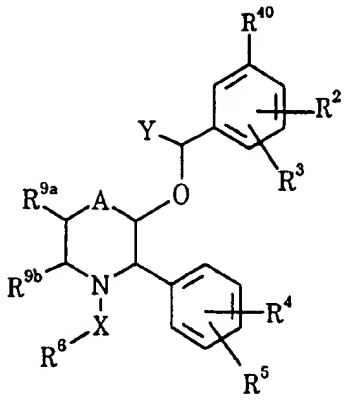
According to another general process (J), compounds of formula (I) wherein m is zero and R^1 is a tetrazol-1-yl group may be prepared by reaction of intermediates of formula (XII)



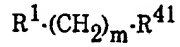
(XII)

with ammonium chloride and sodium azide at elevated temperature, conveniently in a solvent such as dimethylformamide.

According to another general process (K), compounds of formula (I) may be prepared by a coupling reaction between a compound of formula (XX) and (XXI)



(XX)



(XXI)

wherein one of R^{40} and R^{41} is $B(OH)_2$ or $Sn(alkyl)_3$ or a derivative thereof, and the other is a leaving group such as a halogen atom e.g. bromine or iodine, or $-OSO_2CF_3$. Where one of R^{40} and R^{41} is $B(OH)_2$, the reaction is conveniently effected in the presence of a palladium (0) catalyst such as

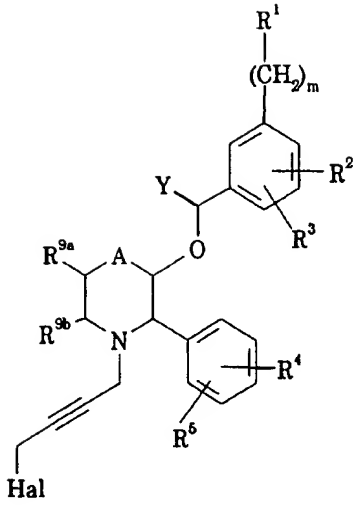
tetrakis(triphenylphosphine)palladium (0) in a suitable solvent such as an ether, for example, dimethoxyethane, at an elevated temperature. Where one of R^{40} and R^{41} is $Sn(alkyl)_3$, the reaction is conveniently effected in the presence of palladium (II) catalyst such as bis(triphenylphosphine) palladium (II) chloride, in a suitable solvent such as an aromatic hydrocarbon, for example, toluene, at an elevated temperature.

Further details of suitable procedures will be found in the accompanying Examples.

Compounds of formula (I) may also be prepared from other compounds of formula (I) using suitable interconversion procedures. For example, compounds of formula (I) wherein X represents C_{1-4}alkyl may be prepared from compounds of formula (I) wherein X represents C_{1-4}alkyl substituted by oxo by reduction, for example, using borane or lithium aluminium hydride. Suitable interconversion procedures will be readily apparent to those skilled in the art.

Intermediates of formula (IV) may be prepared from intermediates of formula (II) by reaction with an acetylene compound of formula $HC{\equiv}C\text{-}CH_2\text{-}Hal$ in the presence of a base such as potassium carbonate in a suitable solvent such as dimethylformamide, conveniently at room temperature, followed by reaction of the resultant acetylene intermediate with an amide of formula $Hal\text{-}CO\text{-}NR^7R^8$ in the presence of suitable catalysts including bis(triphenylphosphine) palladium(II) chloride, copper(I) iodide and triphenylphosphine in a suitable solvent such as triethylamine, preferably at reflux.

Intermediates of formula (V) may be prepared from a compound of formula (XIII)



(XIII)

wherein Hal is a halogen atom, for example, chlorine, bromine or iodine, especially chlorine, by reaction with an azide, for example, sodium azide in a suitable solvent such as dimethylsulphoxide at or below room temperature.

Compounds of formula (XIII) may be prepared by a dropwise addition of an intermediate of formula (II) to a dihaloacetylene of formula Hal-CH_2-C≡C-CH_2-Hal where each Hal is independently chlorine, bromine or iodine, especially chlorine. The reaction is conveniently effected in a suitable solvent such as dimethylformamide in the presence of a base such as potassium carbonate.

Intermediates of formula (VI) may be prepared from intermediates of formula (II) by reaction with a compound of formula Hal-X-C(NH)NH_2, where Hal and X are as previously defined.

Intermediates of formula (VII) may be prepared from intermediates of formula (II) by reaction with a compound of formula Hal-X-C(NH)NHNH-Boc, wherein Hal and X are as previously defined and Boc stands for t-butoxycarbonyl, followed by deprotection under acidic conditions.

Compounds of formula (VIII) are commercially available or may be prepared from commercially available compounds by known methods.

Compounds of formula (IX) may be prepared as described in *J. Med. Chem.*, (1984) 27, 849.

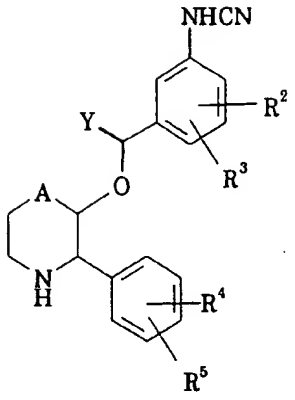
Intermediates of formula (X) may be prepared from the corresponding ester by treatment with hydrazine. The reaction is conveniently effected in a suitable organic solvent, such as an alcohol, for example, ethanol, at elevated temerpature.

For compounds wherein R^6 is a heterocycle substituted by a ZNR^7R^8 group where Z is CH_2, certain favoured compounds of formula (I) may be prepared from a corresponding compound with a hydrogen atom in place of the ZNR^7R^8. Thus, for example a compound of the formula (I) wherein R^6 is an imidazolinone group carrying a $CH_2NR^7R^8$ moiety may be prepared from a corresponding compound lacking the $CH_2NR^7R^8$ moiety by reaction with formaldehyde and an amine NHR^7R^8 under conventional Mannich reaction conditions, for example in methanol with heating. If desired a pre-formed reagent such as $R^7R^8N^+=CH_2.I^-$ may be employed and a tertiary amine such as triethylamine used as acid acceptor.

Alternatively a compound of formula (I) wherein R^6 is an imidazolinone group lacking a $CH_2NR^7R^8$ may be reacted with paraformaldehyde and an amine for example a secondary amine such as pyrrolidine to give a compound wherein the imidazolinone ring is substituted by $CH_2NR^7R^8$ where R^7, R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an oxygen ring atom or a second nitrogen atom which will be part of a NH or NR^c moiety, where R^c is as previously defined.

This reaction may be performed in a conventional manner, for instance, in a suitable solvent such as an alcohol, for example, methanol at an elevated temperature up to the boiling point of the solvent.

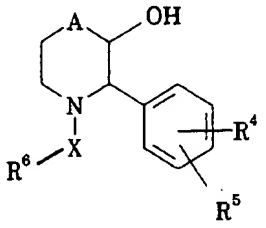
Compounds of formula (XII) may be prepared by reacting a compound of formula (XIV)



(XIV)

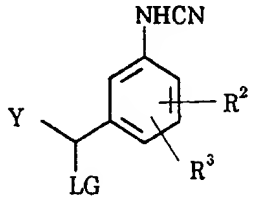
with any suitable reagent for completing the R^6-X- moiety as described in any one of processes (A) to (H).

Alternatively, compounds of formula (XII) may be preapred by reacting a compound of formula (XV)



(XV)

with a compound of formula (XVI)



(XVI)

where LG is a leaving group as previously defined.

Compounds of formula (XX) may be prepared by methods analogous to those described herein.

Compounds of formula (XXI) are known compounds or may be prepared by conventional methodology readily apparent to one of ordinary skill in the art.

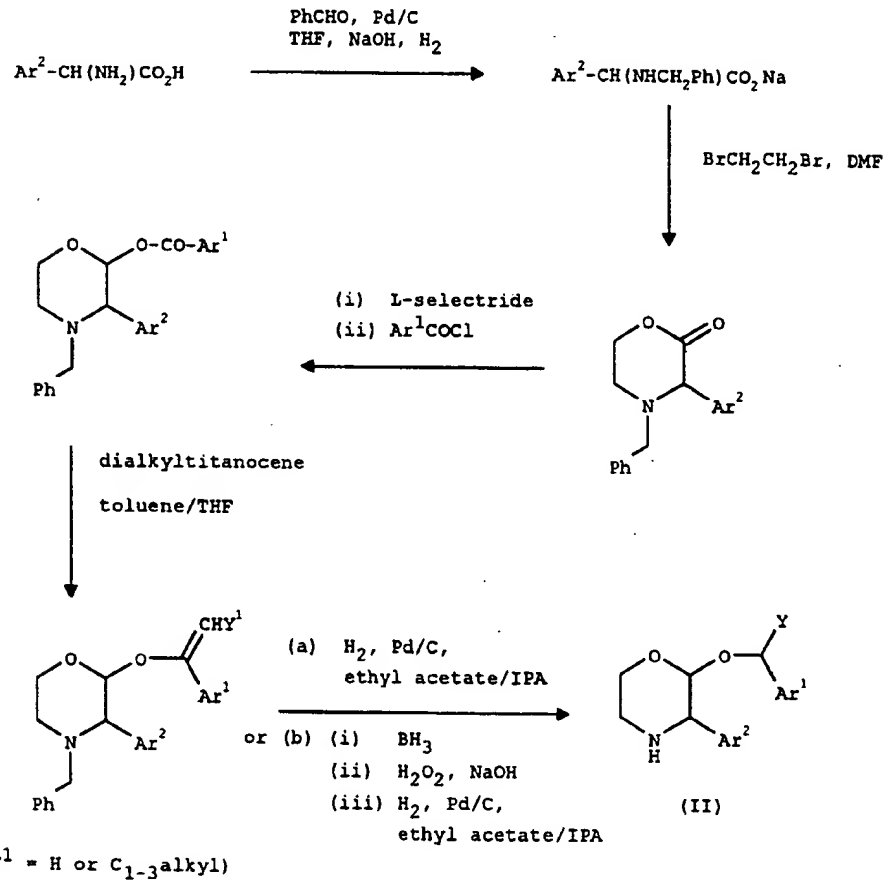
The preferred phosphate prodrugs of the compounds of the present invention are those wherein Y is a derivatized hydroxy substituted C_{1-4}alkyl group. Such preferred compounds may be prepared in a stepwise manner from a compound of formula (I) wherein Y is, for example, $-CH_2OH-$.

Thus, the hydroxy compound is first treated with dibenzyloxydiethylaminophosphine in a suitable solvent such as tetrahydrofuran, preferably in the presence of an acid catalyst such as tetrazole. The resultant compound ($Y = CH_2OP(OCH_2Ph)_2$) is then oxidised using, for example, 4-methylmorpholine-N-oxide to give the dibenzyl-protected phosphate. Deprotection by catalytic hydrogenation or transfer hydrogenation (palladium catalyst on carbon and ammonium formate), in a suitable solvent such as methanol at reflux, yields the desired phosphate prodrug which may be converted to any desired salt form by conventional methodology.

In an alternative two-step method, the hydroxy compound of formula (I) may be reacted with a suitable base such as sodium hydride in tetrahydrofuran, and tetrabenzylpyrophosphate added to yield the dibenzyl-protected phosphate which may be deprotected as described above.

The compounds of the formula (II), wherein A is $-CH_2-$, may be prepared by methods known in the art, for example as described in European patent specification No. 0 528 495-A, published 24th February 1993.

The compounds of the formula (II), wherein A is -O-, may be prepared as shown in the following Scheme in which Ar^1 represents the R^1, R^2, R^3 substituted phenyl group; Ar^2 represents the R^4, R^5 substituted phenyl group and Ph represents phenyl:



L-Selectride is lithium tri-sec-butylborohydride.

The following references describe methods which may be applied by the skilled worker to the chemical synthesis set forth above once the skilled worker has read the disclosure herein:

(i) D.A. Evans *et al.*, *J. Am. Chem. Soc.*, (1990) 112, 4011.

(ii) I. Yanagisawa *et al.*, *J. Med. Chem.*, (1984) 27, 849.

(iii) R. Duschinsky *et al.*, *J. Am. Chem. Soc.*, (1948) 70, 657.

(iv) F.N. Tebbe *et al.*, *J. Am. Chem. Soc.*, (1978) 100, 3611.

(v) N.A. Petasis *et al.*, *J. Am. Chem. Soc.*, (1990) 112, 6532.

(vi) K. Takai *et al., J. Org. Chem.*, (1987) 52, 4412.

The Examples disclosed herein produce predominently the preferred isomers. The unfavoured isomers are also produced as minor components. If desired they may be isolated and employed to prepare the various stereoisomers in conventional manner, for example chromatography using an appropriate column. However, the skilled worker will appreciate that although the Examples have been optimized to the production of the preferred isomers, variation in solvent, reagents, chromatography etc can be readily employed to yield the other isomers.

It will be appreciated that compounds of the formula (I) wherein R^6 contains an =O or =S substituent can exist in tautomeric forms. All such tautomeric forms and mixtures thereof are included within this invention. Most aptly the =O or =S substituent in R^6 is the =O substituent.

Where they are not commercially available, the intermediates of formula (III) above may be prepared by the procedures described in the accompanying Examples or by alternative procedures which will be readily apparent to one skilled in the art.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The exemplified compounds of this invention were tested by the methods set out at pages 36 to 39 of International Patent Specification No. WO 93/01165. The compounds or, in the case of prodrugs, the parent compounds, were found to be active with IC_{50} at the NK_1 receptor of less than 100nM on said test method.

The following non-limiting Examples further illustrate the present invention:

DESCRIPTION 1

[2*S*,3*S*]-1-*tert*-Butoxycarbonyl-2-phenyl-3-[3-bromo-5-(trifluoromethyl) phenylmethoxy]piperidine

(i) Methyl 3-nitro-5-(trifluoromethyl)benzoate

3-Nitro-5-trifluoromethylbenzoic acid (5.0g) was added to methanolic hydrogen chloride (saturated, 10ml) and the mixture was stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure, water was added and the mixture was extracted with ethyl acetate. The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexane (30:70) to give *methyl 3-nitro-5-(trifluoromethyl)benzoate* as a yellow oil (3.6g), ^1H NMR (360MHz,$CDCl_3$) δ 4.04 (3H, s), 8.61 (1H, s), 8.67 (1H, s), and 9.05 (1H, s).

(ii) Methyl 3-amino-5-(trifluoromethyl)benzoate

Tin (II) chloride (60g) was added to a solution of methyl 3-nitro-5-(trifluoromethyl)benzoate (25g, 100mmol) in ethanol (600ml) and the mixture was heated to 60°C for 2 hours. The mixture was cooled and concentrated under reduced pressure to approximately one third volume. The mixture was added slowly to saturated aqueous sodium hydrogen carbonate (1000ml) and the resulting mixture was filtered through celite. The filter cake was washed with ethyl acetate (500ml). The organic layer was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give *methyl 3-amino-5-(trifluoromethyl)benzoate* as an orange solid (12.4g), ^1H NMR (360MHz,$CDCl_3$) δ 3.95 (3H, s), 7.08 (1H, br s), 7.51 (1H, s), and 7.66 (1H, s).

(iii) Methyl 3-bromo-5-(trifluoromethyl)benzoate

Methyl 3-amino-5-(trifluoromethyl)benzoate (2.2g) in dry acetonitrile (5ml) was added dropwise to a solution of copper (II) bromide (2.68g) and *tert*-butyl nitrite (1.78ml) in dry acetonitrile stirring at 65°C under a dry nitrogen atmosphere. After 30 minutes at 65°C the reaction mixture was cooled to room temperature and poured into 2N aqueous HCl (50ml) and extracted into ethyl acetate (100ml). The organic layers were separated, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give *methyl 3-bromo-5-(trifluoromethyl) benzoate* as a clear oil (2.69g). ^1H NMR (360MHz,$CDCl_3$) δ 3.97 (3H,s), 7.83 (1H, s), 7.98 (1H, s), 8.46 (1H, s).

(iv) 3-Bromo-5-(trifluoromethyl)benzyl alcohol

Lithium borohydride (220mg) was added in a single portion to a stirred solution of methyl 3-bromo-5-(trifluoromethyl)benzoate (2.46g) in ether (60ml) containing water (156ml). The resulting solution was stirred for 4 hours at room temperature, at which point the reaction mixture was diluted with saturated aqueous NH_4Cl solution (50ml). The organic layers were separated, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give *3-bromo-5-(trifluoromethyl)benzyl alcohol* as a clear oil (2.1g).^1H NMR (360MHz,$CDCl_3$) δ 1.83 (1H, br s), 4.76 (2H,s), 7.47 (1H, s), 7.56 (1H, s), 7.68 (1H, s).

(v) 1-(Methanesulfonyloxymethyl)-3-bromo-5-trifluoromethylbenzene

Methanesulfonyl chloride (342mg) was added dropwise to a stirred solution of 3-bromo-5-(trifluoromethyl)benzyl alcohol (560mg) and triethylamine (417μl) in dry dichloromethane (20ml) at -78°C under a dry nitrogen atmosphere. The reaction was maintained at -78°C for 30 minutes and then allowed to warm to room temperature over 2 hours. After this period the reaction mixture was diluted with 5% aqueous citric

acid and the organic layers were separated, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give *1-(methanesulfonyloxymethyl)-3-bromo-5-(trifluoromethyl)benzene* as a yellow oil (480mg) ^1H NMR (360MHz,$CDCl_3$) δ 3.06 (3H,s),5.24 (2H, s), 7.59 (1H, s), 7.75 (1H, s), 7.94 (1H, s).

(vi) [2*S*,3*S*]-1-*tert*-Butoxycarbonyl-2-phenyl-3-[3-bromo-5-(trifluoromethyl)phenylmethoxy]piperidine

Sodium hydride (56mg of a 60% dispersion in oil) was added to a stirred solution of [2*S*,3*S*]-N-*tert*-butoxycarbonyl-2-phenylpiperidine-3-ol (332mg) in dry N,N-dimethylformamide (10.0ml) under a dry nitrogen atmosphere. After 30 minutes 1-(methanesulfonyloxymethyl)-3-bromo-5-(trifluoromethyl)benzene (480mg) was added, and the reaction was stirred for 18hours at room temperature. The resulting mixture was then diluted with water (50ml), and extracted into ethyl acetate (2x50ml). The organic layers were separated and washed with brine (20ml), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by MPLC (20% ethyl acetate/n-hexane), afforded *[2S,3S]-1-tert-butoxycarbonyl-2-phenyl-3-[(3-bromo-5-(trifluoromethyl)phenylmethoxy] piperidine* as a yellow gum (370mg). ^1H NMR (360MHz,$CDCl_3$) δ 1.46 (9H, s), 1.63 (2H, m), 1.99 (2H, m), 2.74 (1H, t d, J=7.2, 3.0Hz), 3.81 (1H,m), 3.92 (1H, m), 4.63 (2H, d, J=5.0Hz), 5.67 (1H, br s), 7.23 (2H, m), 7.34 (2H, m), 7.45 (1H, s), 7.53 (2H, d, J=5.0Hz), 7.65 (1H, s).

DESCRIPTION 2

1-Methyl-5-tributylstannanyl-1H-[1,2,3]triazole

A solution of 1-methyl-1H-[1,2,3]triazole (350mg) in dry tetrahydrofuran (5.0ml) was added dropwise under nitrogen to a stirred, cooled (-78°C) solution of n-butyl lithium (2.81ml of 1.6M solution in hexanes) in dry tetrahydrofuran (10ml). After 1 hour tributylchlorostannane (1.46g) was added. The reaction was maintained

at -78°C for 30min. and then allowed to warm to room temperature over 2 hours. The reaction mixture was diluted with brine (10ml) and extracted into ethyl acetate (50ml). The organic layer was separated, washed with brine (50ml), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (20% ethyl acetate/n-hexane), to give *1-methyl-5-tributylstannanyl-1H-[1,2,3]triazole* as a yellow oil (1.03g). ^1H NMR (360MHz,$CDCl_3$) δ 0.87 (9H, m), 1.15 (6H, m), 1.28 (6H, m), 1.36 (6H, m), 4.02 (3H, s), 7.60 (1H, s); MS m/z CI^+ 372 ($M+H^+$).

DESCRIPTION 3

[2*S*,3*S*]-2-Phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl) phenylmethoxy]piperidine hydrochloride

(i) [2*S*,3*S*]-1-*tert*-Butoxycarbonyl-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine

Bis(triphenylphosphine)palladium dichloride (5.0mg) was added to a degassed solution of [2*S*,3*S*]-1-*tert*-butoxycarbonyl-2-phenyl-3-[3-bromo-5-(trifluoromethyl)phenylmethoxy]piperidine (330mg), and 1-methyl-5-tributylstannanyl-1H-[1,2,3]triazole (713mg) in dry toluene (15.0ml) under a dry nitrogen atmosphere. The resulting solution was warmed to reflux for 4 hours. After this time the reaction was cooled to room temperature and the solvent removed under reduced pressure. The residue was partitioned between aqueous $NaHCO_3$ solution (10ml, satd.) and ethyl acetate. The organic layer was washed with brine (10ml), dried over $MgSO_4$, filtered and the solvent removed under pressure. Purification by MPLC (1:1 ethyl acetate/n-hexane) afforded *[2S,3S]-1-tert-butoxycarbonyl-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine* as a yellow foam (330mg). ^1H NMR (360MHz,$CDCl_3$) δ 1.45 (9H, s), 1.74 (2H, m), 2.00 (2H, m), 2.75 (1H,

t d, J=7.2, 3.0Hz), 3.91 (2H,m), 4.03 (3H, s), 4.74 (2H, s), 5.71 (1H, br s), 7.27-7.33 (3H, m), 7.44-7.62 (5H, m), 7.75 (1H, s).

(ii) [2*S*,3*S*]-2-Phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine hydrochloride

A solution of HCl in ethanol (2ml, 5N) was added to a stirred solution of [2*S*,3*S*]-1-*tert*-butoxycarbonyl-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl)]phenylmethoxy]piperidine (330mg) in dry ethanol. After 2 hours the solvent was removed under reduced pressure to give *[2S,3S]-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl)-phenylmethoxy] piperidine hydrochloride* as a white solid (270mg). ^{1}H NMR (360MHz, D_2O) δ 1.79-1.88 (2H, m), 2.11 (1H, m), 2.340 (2H, m), 3.21 (1H, m), 3.7 (1H, m), 3.93 (3H, s), 3.96 (1H, br s), 4.11 (1H, s), 4.42 (1H, d, J=11.0Hz), 4.74 (1H, d, J=11.0Hz), 6.93 (1H, s), 7.05 (1H, m), 7.24 (4H, m), 7.65 (1H, d, J=4.0Hz), 7.70 (1H, s), 7.80 (1H, s).

DESCRIPTION 4

[2*S*,3*S*]-1-*tert*-Butoxycarbonyl-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine

(i) Methyl 3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)benzoate

Triethylorthoacetate (2.57ml, 14mmol) was added to a stirred, heated (75°C) solution of methyl 3-amino-5-(trifluoromethyl)benzoate (the product of Description 1, step ii) (2.19g, 10mmol) in acetic acid (15ml). The mixture was stirred at 75°C for 45 minutes, then sodium azide (1.95g, 30mmol) was added in portions over 45 minutes. The mixture was stirred at 75°C for 4 hours, cooled and poured into water (50ml). The pH was adjusted to 7.0 with aqueous sodium hydroxide (4M) and the mixture was extracted with ethyl acetate (3 x 50ml). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (2 x 50ml) and brine (50ml), dried ($MgSO_4$) and the solvent was evaporated

under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexane (30:70 increasing to 60:40) to give *methyl 3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)benzoate* as a yellow oil (1.62g, 57%), ^{1}H ($CDCl_3$) δ 8.51 (1H, s), 8.36 (1H, s), 8.02 (1H, s), 4.03 (3H, s), and 2.71 (3H, s). m/z 287 ($M+H^+$).

(ii) 3-(5-Methyltetrazol-1-yl)-5-(trifluoromethyl)phenylmethanol

Methyl 3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)benzoate (1.56g, 5.5mmol) was dissolved in ether (20ml) and cooled in ice. Water (98ml, 98mg, 5.5mmol) then lithium borohydride (131mg, 6mmol) were added and the mixture was stirred at room temperature for 1 hour. Tetrahydrofuran (10ml) was added and the mixture was stirred at room temperature for 1 hour. Methanol (5ml) was added and the solvent was evaporated under reduced pressure. Saturated aqueous sodium hydrogen carbonate (20ml) and water (10ml) were added and the mixture was extracted with dichloromethane (10 x 10ml). The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by MPLC on silica gel, eluting with ethyl acetate/hexane (50:50 increasing to 100:0) to give *3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)phenylmethanol* as a colorless oil (1.00 g, 70%), ^{1}H ($CDCl_3$) δ 7.84 (1H, s), 7.75 (1H, s), 7.67 (1H, s), 4.92 (2H, s), 2.67 (3H, s), and 1.86 (1H, br s). m/z 259 ($M+H^+$).

(iii) 1-(Methanesulfonyloxymethyl)-3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)benzene

Methanesulfonyl chloride (0.26ml, 0.39g, 3.4mmol) was added dropwise to a stirred, cooled (-30°C) solution of 3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)phenylmethanol (725mg, 2.8mmol) and triethylamine (0.59ml, 0.43g, 4.2mmol) in dichloromethane (15ml). The mixture was stirred at -30°C for 45 minutes, diluted with dichloromethane (20ml),

washed with aqueous citric acid (10%, 20ml) and saturated aqueous sodium hydrogen carbonate (20ml), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give *1-(methanesulfonyloxymethyl)-3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)benzene* as a yellow oil (877mg, 93%), ^1H ($CDCl_3$) δ 7.86 (1H, s), 7.81 (2H, s), 5.38 (2H, s), 3.14 (3H, s), and 2.69 (3H, s).

(iv) [2*S*,3*S*]-1-*tert*-Butoxycarbonyl-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine

Sodium hydride (60% dispersion in mineral oil, 24mg, 0.6mmol) was added to a stirred, cooled (0°C) solution of [2*S*,3*S*]-1-*tert*-butoxycarbonyl-2-phenylpiperidin-3-ol (138mg, 0.5mmol) in N,N-dimethylformamide (2ml). The mixture was stirred at room temperature for 30 minutes, cooled in ice and 1-(methanesulfonyloxymethyl)-3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)benzene (168mg, 0.5mmol) in N,N-dimethylformamide (2ml) was added. The mixture was stirred at room temperature for 66 hours, saturated aqueous sodium hydrogen carbonate (20ml) and water (10ml) were added and the mixture was extracted with ethyl acetate (3 x 20ml). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (4 x 20ml) and brine (20ml), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by MPLC on silica gel, eluting with ethyl acetate/hexane (40:60 increasing to 60:40) to give *[2S,3S]-1-tert-butoxycarbonyl-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl) phenylmethoxy]piperidine* as a pale yellow oil (133mg, 51%), ^1H ($CDCl_3$) δ 7.69 (1H, s), 7.65 (1H, s), 7.52 (3H, m), 7.31-7.19 (3H, m), 5.68 (1H, br s), 4.77 (2H, s), 3.92 (2H, m), 2.78 (1H, m), 2.58 (3H, s), 2.00 (2H, m), 1.66 (2H, m), and 1.45 (9H, s). m/z 518 ($M+H^+$).

EXAMPLE 1

[2*S*,3*S*]-1-[(5-(Dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl)-phenylmethoxy]piperidine

(i) [2*S*,3*S*]-1-(4-Chlorobut-2-yn-1-yl)-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine

A solution of [2*S*,3*S*]-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine hydrochloride (270mg) in N,N-dimethylformamide (3.0ml) was slowly added to a solution of 1,4-dichlorobut-2-yne (189ml) and potassium carbonate (269mg) in N,N-dimethylformamide (5.0ml). The solution was stirred for 18 hours at room temperature and the solvent removed under reduced pressure. To the residue was added water (40ml) and the product was extracted with ethyl acetate (3x10ml). The combined organic fractions were washed with water, saturated brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was purified by MPLC (40% ethyl acetate/hexane) to give *[2S,3S]-1-(4-chlorobut-2-yn-1-yl)-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl) phenylmethoxy]piperidine* as a yellow oil (142mg). ^{1}H NMR (360MHz,$CDCl_3$) δ 1.52 (2H, m), 2.16 (2H, m), 2.64 (1H, m), 3.00 (1H, m), 3.30 (2H, m), 3.48 (1H, br s), 3.57 (1H, s), 3.98 (3H, s), 4.11 (1H, d, J=11.0Hz), 4.15 (1H, s) 4.52 (2H, d, J=11.0Hz), 7.17-7.26 (4H, m), 7.40-7.47 (4H, m), 7.68 (1H, s).

(ii) [2*S*,3*S*]-1-(4-Azidobut-2-yn-1-yl)-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine

To a solution of [2*S*,3*S*]-1-(4-chlorobut-2-yn-1-yl)-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl)phenylmethoxy] piperidine (142mg) in dimethyl sulphoxide (3.0ml) was added sodium azide (20.1mg). The solution was stirred for 3 hours at room temperature

at which time aqueous ammonium chloride and ethyl acetate were added. The organic phase was separated, washed with water (20ml), saturated brine (20ml) dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by MPLC (20% ethyl acetate/hexane) gave *[2S,3S]-1-(4-azidobut-2-yn-1-yl)-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine* as a white solid (120mg). ^{1}H NMR (360MHz,$CDCl_3$) δ 1.20-1.60 (2H, m), 2.22 (2H, m), 2.67 (1H, m), 2.98 (1H, m), 3.27 (2H, m), 3.47 (1H, br s), 3.62 (1H, br s), 3.92 (2H, s), 3.98 (3H, s), 4.47 (1H, d, J=11.0Hz), 4.81 (1H, d, J=11.0Hz), 7.26-7.35 (4H, m), 7.44-7.47 (4H, m), 7.69 (1H, s).

(iii) [2*S*,3*S*]-1-{[5-(Dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl]methyl]}-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl) phenylmethoxy]piperidine

Dimethylamine (approximately 10ml) was condensed at -80°C in a pressure tube and to this was added a solution of [2*S*,3*S*]-1-(4-azidobut-2-yn-1-yl)-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl) phenylmethoxy]piperidine (138mg) in dioxan (5ml). The tube was sealed and the solution was heated at 80°C for 18 hours. The solvent was evaporated under reduced pressure to dryness and the residue was purified by MPLC [5% methanol in dichloromethane containing 0.25% ammonia (SG. 0.88)] to give *[2S,3S]-1-[(5-(dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine* as a clear oil (68mg). ^{1}H NMR (250MHz,$CDCl_3$) δ 1.41-1.58 (2H, m), 1.95 (2H, m), 2.17 (6H, s), 2.27 (1H, m), 3.10 (1H, m), 3.23 (4H, m), 3.57 (1H, br s), 3.81 (1H, d, J=14.0Hz), 3.98 (3H, s), 4.25 (1H, d, J=13.0Hz), 4.54 (1H, d, J=13.0Hz), 7.00-7.23 (4H, m), 7.32-7.49 (4H, m), 6.79 (1H, s), 7.78 (1H, s). MS m/z 555 CI^+ ($M+H^+$).

EXAMPLE 2

[2*S*,3*S*]-1-[(5-(Dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl) phenylmethoxy]piperidine

(i) [2*S*,3*S*]-1-(4-Chlorobut-2-yn-1-yl)-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine

A solution of HCl in ethanol (5M, 4ml) was added to a stirred solution of [2*S*,3*S*]-1-*tert*-butoxycarbonyl-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine (125mg, 0.24mmol) in ethanol (2ml). The mixture was stirred at room temperature for 90 minutes and the solvent was evaporated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (3ml) and potassium carbonate (100mg, 0.72mmol) and 1,4-dichlorobut-2-yne (47ml, 59mg, 0.48mmol) were added. The mixture was stirred at room temperature for 16 hours. Further potassium carbonate (100mg, 0.72mmol) and 1,4-dichlorobut-2-yne (47ml, 59mg, 0.48mmol) were added and the mixture was stirred at 50°C for 2 hours. Further potassium carbonate (100mg, 0.72mmol) and 1,4-dichlorobut-2-yne (47ml, 59mg, 0.48mmol) were added and the mixture was stirred at 50°C for 1 hours. The mixture was cooled to room temperature, saturated aqueous sodium hydrogen carbonate (20ml) and water (10ml) were added and and the mixture was extracted with ethyl acetate (3 x 20ml). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (4 x 20ml) and brine (20ml), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate/hexane (50:50 increasing to 80:20) to give *[2S,3S]-1-(4-chlorobut-2-yn-1-yl)-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine* as a yellow oil (90 mg, 74%) ^1H ($CDCl_3$) δ 7.54 (2H, s), 7.44-7.06 (6H, m), 4.63

(1H, d, J=12.9Hz), 4.16 (3H, m), 3.61-3.22 (4H, m), 3.04 (1H, m), 2.65 (1H, m), 2.55 (3H, s), 2.21 (2H, m), and 1.63 (2H, m). m/z 504 ($M+H^+$).

(ii) [2*S*,3*S*]-1-(4-Azidobut-2-yn-1-yl)-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine

Sodium azide (14mg, 0.21mmol) was added to a solution of [2*S*,3*S*]-1-(4-chlorobut-2-yn-1-yl)-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine (90mg, 0.18mmol) in dimethyl sulphoxide (3ml) and the solution was stirred at room temperature for 16 hours. Saturated aqueous sodium hydrogen carbonate (20ml) and water (10ml) were added and and the mixture was extracted with ethyl acetate (3 x 20ml). The combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (4 x 20ml) and brine (20ml), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give *[2S,3S]-1-(4-azidobut-2-yn-1-yl)-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine* as a yellow oil (89mg, 98%) ^1H ($CDCl_3$) δ 7.54 (2H, s), 7.43-7.08 (6H, m), 4.62 (1H, d, J=13.2Hz), 4.18 (1H, d, J=13.2Hz), 3.92 (2H, s), 3.61-3.30 (4H, m), 3.02 (1H, m), 2.69 (1H, m), 2.55 (3H, s), 2.14 (2H, m), and 1.62 (2H, m). m/z 511 ($M+H^+$).

(iii) [2*S*,3*S*]-1-[(5-(Dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl) methyl]-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl) phenylmethoxy] piperidine

Liquid dimethylamine (10ml) was added to a solution of [2*S*,3*S*]-1-(4-azidobut-2-yn-1-yl)-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine (89mg, 0.17ml) in 1,4-dioxane (2ml). The tube was sealed and the mixture was heated at 80°C for 20 hours. The mixture was cooled and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/methanol/ aqueous ammonia (92/8/0.8 increasing to 90/10/1) to give *[2S,3S]-1-[(5-*

(dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)phenylmethoxy]piperidine as an off white foam (54mg, 56%) ^{1}H ($CDCl_3$) δ 7.55-7.45 (4H, m), 7.22 (2H, m), 7.10 (2H, m), 4.62 (1H, d, J=13.0Hz), 4.17 (1H, d, J=13.0Hz), 3.81 (1H, d, J=14.4Hz), 3.57-3.37 (5H, m), 3.09 (1H, m), 2.56 (3H, s), 2.41-1.90 (4H, m), 2.23 (6H, s), and 1.56 (2H, m). m/z 556 ($M+H^+$).

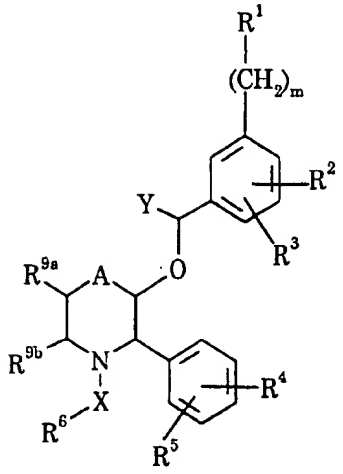
EXAMPLE 3

[2*S*,3*S*]-1-[(5-(Dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)phenylmethoxy] piperidine dihydrochloride

A solution of HCl in ethanol (5M, 43ml) was added to a stirred, cooled solution of [2*S*,3*S*]-1-[(5-(dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl) phenylmethoxy]piperidine (49mg, 90mmol) in ethanol (2ml). The solvent was evaporated under reduced pressure and the residue was triturated with ether (5ml). The solid was collected and dried *in vacuo* to give *[2S,3S]-1-[(5-(dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[3-(5-methyltetrazol-1-yl)-5-(trifluoromethyl)phenylmethoxy] piperidine dihydrochloride* as a tan-coloured solid (55mg), mp 134-137°C, ^{1}H (D_2O) δ 7.78 (3H, m), 7.44-7.00 (7H, m), 4.87 (1H, d, J=13.5Hz), 4.47 (1H, d, J=13.5Hz), 4.40 (1H, d, J=15.3Hz), 4.36 (1H, d, J=15.3Hz), 4.30 (1H, s), 3.83-3.61 (5H, m), 3.29 (1H, d, J=14.6Hz), 2.67 (6H, s), 2.51 (3H, s), 2.31 (2H, m), 1.85 (1H, m), and 1.71 (1H, m).

CLAIMS:

1. A compound of the formula (I):



(I)

wherein

R^1 is a 5- or 6-membered aromatic heterocyclic group containing 1, 2, 3 or 4 heteroatoms selected from nitrogen, oxygen and sulphur, which group is optionally substituted by one or two substituents selected from C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, SR^x, SOR^x, SO_2R^x, phenyl, NR^aR^b, NR^aCOR^x, CH_2COCF_3 and CF_3, where R^a and R^b are independently hydrogen or C_{1-4}alkyl and R^x is C_{1-4}alkyl;

R^2 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, CF_3, OCF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, where R^a and R^b each independently represent hydrogen or C_{1-4}alkyl;

R^3 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or CF_3;

R^4 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, CF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, where R^a and R^b each independently represent hydrogen or C_{1-4}alkyl;

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or CF_3;

R^6 is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O, =S or a C_{1-4}alkyl group, and optionally substituted by a group of the formula ZNR^7R^8 where

Z is C_{1-6}alkylene or C_{3-6}cycloalkylene;

R^7 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-7}cycloalkylC_{1-4}alkyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxyl;

R^8 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-7}cycloalkylC_{1-4}alkyl, or C_{2-4}alkyl substituted by one or two substituents selected from C_{1-4}alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

or R^7, R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy or C_{1-4}alkyl optionally substituted by a C_{1-4}alkoxy or hydroxyl group, and optionally containing a double bond, which ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or $S(O)_2$ or a second nitrogen atom which will be part of a NH or NR^c moiety where R^c is C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy;

or R^7, R^8 and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

or Z, R^7 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

R^{9a} and R^{9b} are each independently hydrogen or C_{1-4}alkyl, or R^{9a} and R^{9b} are joined so, together with the carbon atoms to which they are attached, there is formed a C_{5-7} ring;

A is -O- or $-CH_2-$;

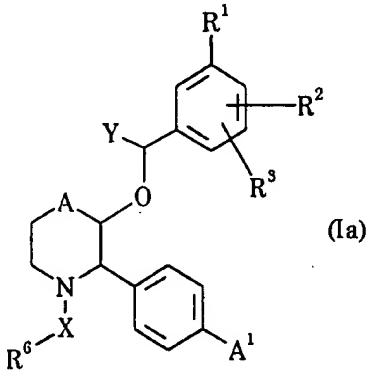
X is an alkylene chain of 1 to 4 carbon atoms optionally substituted by oxo;

Y is hydrogen or a C_{1-4}alkyl group optionally substituted by a hydroxyl group; and

m is zero or 1;

or a pharmaceutically acceptable salt or prodrug thereof.

2. A compound as claimed in claim 1 of the formula (Ia) or a pharmaceutically acceptable salt or prodrug thereof:

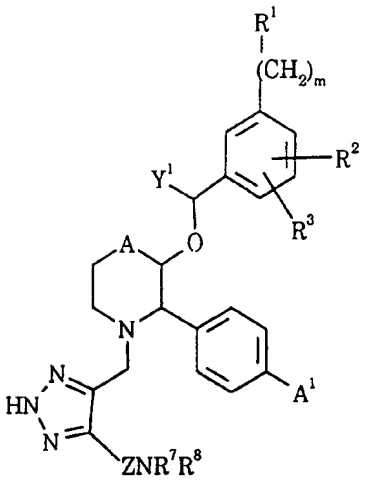


(Ia)

wherein

A, X, Y, R^1, R^2, R^3 and R^6 are as defined in claim 1 and A^1 is fluorine or hydrogen.

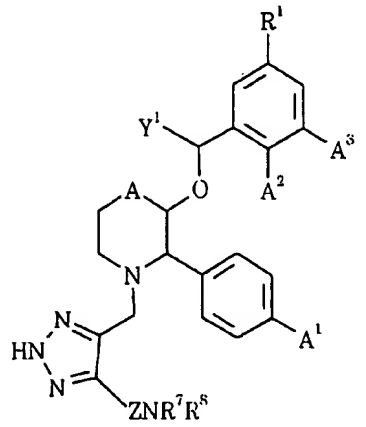
3. A compound as claimed in claim 1 of the formula (Ib) or a pharmaceutically acceptable salt thereof:



(Ib)

wherein A, Z, R^1, R^2, R^3, R^7, R^8 and m are as defined in claim 1, A^1 is fluorine or hydrogen, and Y^1 is hydrogen or methyl.

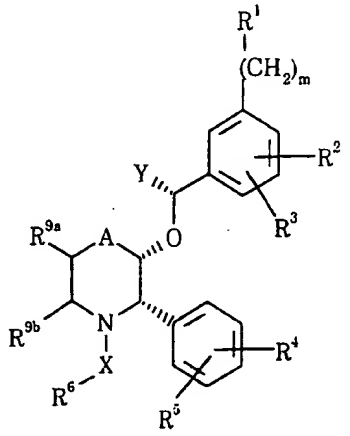
4. A compound as claimed in claim 1 of the formula (Ic) or a pharmaceutically acceptable salt thereof:



(Ic)

wherein R^1, R^7, R^8 and Z are as defined in claim 1; Y^1 is hydrogen or methyl; A^1 is fluorine or hydrogen; A^2 is hydrogen, C_{1-4}alkoxy, halogen, CF_3 or OCF_3; and A^3 is hydrogen, halogen or CF_3.

5. A compound as claimed in claim 1 of the formula (Id) or a pharmaceutically acceptable salt or prodrug thereof:

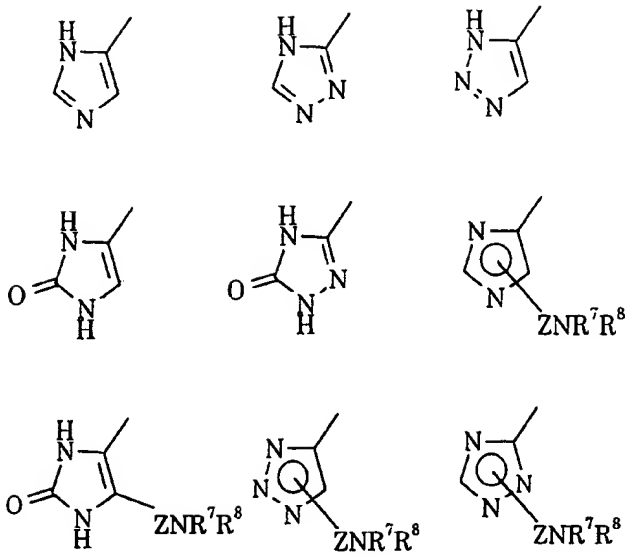


(Id)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^{9a}, R^{9b}, A, X, Y and m are as defined in claim 1.

6. A compound as claimed in claim 1 wherein X represents CH_2, $CH(CH_3)$ or CH_2CH_2.

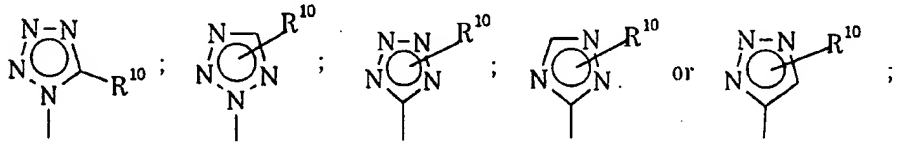
7. A compound as claimed in claim 1 wherein R^6 represents a heterocyclic ring selected from:



wherein Z, R^7 and R^8 are as defined in claim 1.

8. A compound as claimed in claims 1 to 7 wherein Z is CH_2 or CH_2CH_2 and NR^7R^8 is amino, methylamino, dimethylamino, diethylamino, azetidinyl, pyrrolidino and morpholino.

9. A compound as claimed in any one of claims 1 to 8 wherein R^1 is a group selected from



where R^{10} is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, SR^x, SOR^x, SO_2R^x, phenyl, NR^aR^b, NR^aCOR^x, CH_2COCF_3 or CF_3, where R^a and R^b are independently hydrogen or C_{1-4}alkyl, and R^x is C_{1-4}alkyl.

10. A compound as claimed in claim 1 wherein m is zero.

11. A compound selected from:
[2*S*,3*S*]-1-[(5-(dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[3-(1-methyl-1H-[1,2,3]triazol-5-yl)-5-(trifluoromethyl)-phenylmethoxy]piperidine;
[2*S*,3*S*]-1-[(5-(dimethylaminomethyl)-1H-[1,2,3]triazol-4-yl)methyl]-2-phenyl-3-[3-(5-methyl-1H-tetrazol-1-yl)-5-(trifluoromethyl)-phenylmethoxy]piperidine;
or a pharmaceutically acceptable salt or prodrug thereof.

12. A compound as claimed in any preceding claim for use in therapy.

13. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 11 in association with a pharmaceutically acceptable carrier or excipient.

14. A method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof.

15. A method according to claim 14 for the treatment or prevention of pain or inflammation.

16. A method according to claim 14 for the treatment or prevention of migraine.

17. A method according to claim 14 for the treatment or prevention of emesis.

18. A method according to claim 14 for the treatment or prevention of postherpetic neuralgia.

19. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of a physiological disorder associated with an excess of tachykinins.

20. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of pain or inflammation.

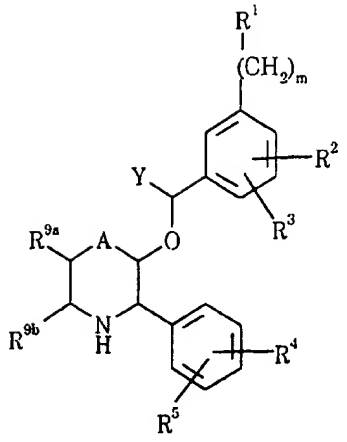
21. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of migraine.

22. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of emesis.

23. The use of a compound as claimed in any one of claims 1 to 11 for the manufacture of a medicament for the treatment or prevention of postherpetic neuralgia.

24. A process for the preparation of a compound as claimed in claim 1 which comprises:

(A) reaction of a compound of formula (II)



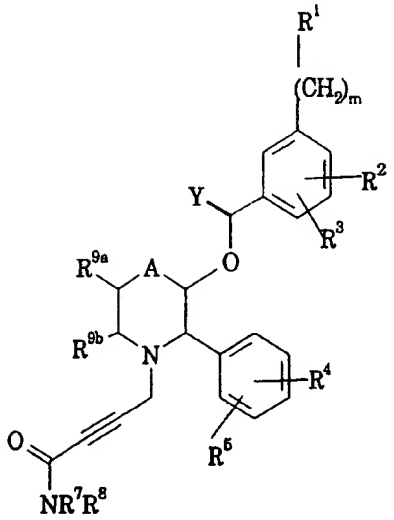
(II)

wherein R^1, R^2, R^3, R^4, R^5, R^{9a}, R^{9b}, A, Y and m are as defined in claim 1 with a compound of formula (III):

$$X^1\text{-}X\text{-}R^{6a} \qquad \text{(III)}$$

where X is as defined in claim 1, R^{6a} is a group of the formula R^6 as defined in claim 1 or a precursor therefor and X^1 is a leaving group; and, if R^{6a} is a precursor group, converting it to a group R^6; or

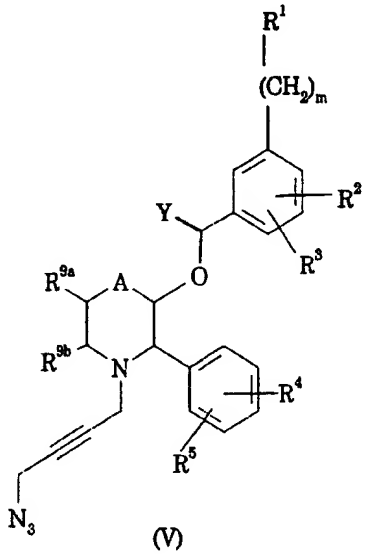
(B), for compounds of formula (I) wherein R^6 represents 1,2,3-triazol-4-yl substituted by $CH_2NR^7R^8$, and X is $-CH_2-$, reaction of a compound of formula (IV)



(IV)

with an azide, followed by reduction of the carbonyl group adjacent to -NR^7R^8 using a suitable reducing agent; or

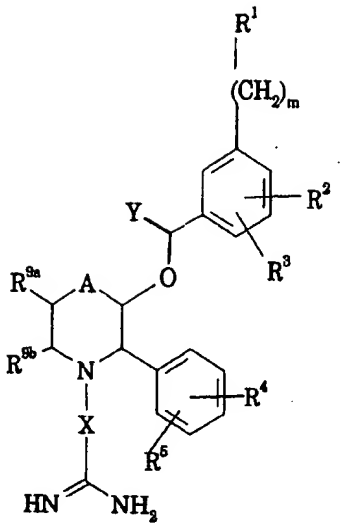
(C), for compounds of formula (I) wherein R^6 represents 1,2,3-triazol-4-yl substituted by CH2NR^7R^8, and X is -CH_2-, reaction of a compound of formula (V)



(V)

with an amine of formula NHR^7R^8; or

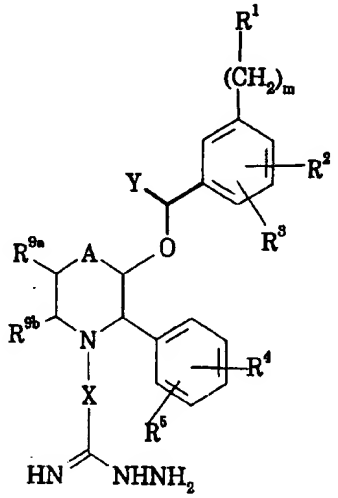
(D), for compounds of formula (I) wherein R^6 represents substituted or unsubstituted 1,3,5-triazine, reaction of intermediates of formula (VI):



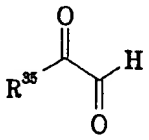
(VI)

with substituted or unsubstituted 1,3,5-triazine; or

(E), for compounds of formula (I) wherein R^6 represents substituted or unsubstituted 1,2,4-triazine, reaction of an intermediate of formula (VII) with a dicarbonyl compound of formula (VIII):



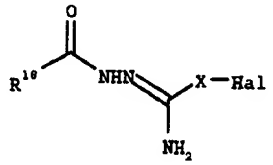
(VII)



(VIII)

wherein R^{35} represents H or a suitable substituent such as ZNR^7R^8; or

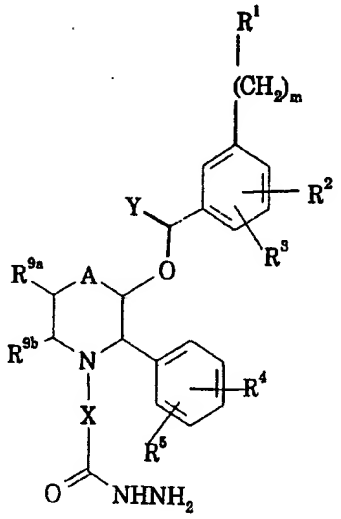
(F), for compounds of formula (I) wherein R^6 represents a substituted 1,2,4-triazolyl group, reaction of an intermediate of formula (II) with a compound of formula (IX)



(IX)

wherein X is as defined in claim 1, Hal is a halogen atom, and R^{18} is H, $CONH_2$ or OCH_3 (which is converted to an oxo substituent under the reaction conditions), in the presence of a base, followed where necessary by conversion to a compound of formula (I); or

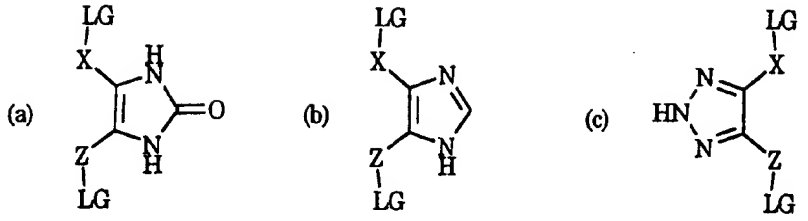
(G), for compounds of formula (I) wherein R^6 represents thioxotriazolyl, reaction of an intermediate of formula (X)



(X)

with a compound of formula HNCS, in the presence of a base; or

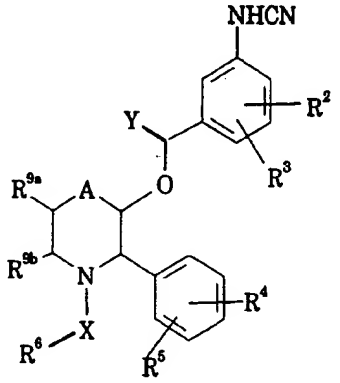
(H), for compounds of formula (I) wherein the heterocycle R^6 is substituted by ZNR^7R^8, reaction of an intermediate of formula (II) as defined above with one of the compounds of formula (XI):



(XI)

wherein each LG, which may be the same or different, is a leaving group, and X and Z are as defined in claim 1, followed by reaction of the resultant compound with an amine NHR^7R^8 to complete the ZNR^7R^8 moiety; or

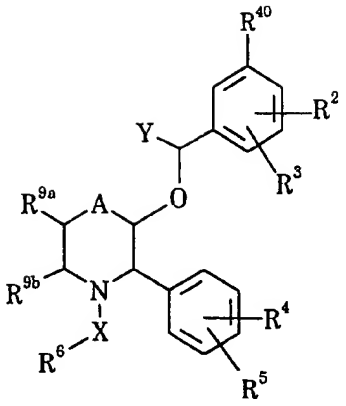
(J), for compounds of formula (I) wherein m is zero and R^1 is a tetrazol-1-yl group, reaction of an intermediate of formula (XII):



(XII)

with ammonium chloride and sodium azide at elevated temperature; or

(K), a coupling reaction between a compound of formula (XX) and (XXI)



(XX)

R^1-$(CH_2)_m$-R^{41}

(XXI)

wherein one of R^{40} and R^{41} is $B(OH)_2$ or $Sn(alkyl)_3$ or a derivative thereof, and the other is a leaving group, in the presence of a palladium catalyst;

each process being followed, where necessary, by the removal of any protecting group where present;

and when the compound of formula (I) is obtained as a mixture of enantiomers or diastereoisomers, optionally resolving the mixture to obtain the desired enantiomer;

and/or, if desired, converting the resulting compound of formula (I) or a salt thereof, into a pharmaceutically acceptable salt or prodrug thereof.

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/GB 96/01478

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D403/14 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 19323 (MERCK SHARP & DOHME ;BAKER RAYMOND (GB); SWAIN CHRISTOPHER JOHN (G) 1 September 1994 see abstract; claim 3 ---	1-24
A	EP,A,0 577 394 (MERCK & CO INC) 5 January 1994 cited in the application see abstract; claims 5,7 ---	1-24
A	WO,A,95 08549 (GLAXO GROUP LTD ;ARMOUR DUNCAN ROBERT (GB); EVANS BRIAN (GB); GIBL) 30 March 1995 cited in the application see abstract; claims --- -/--	1-24

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 1996	23.10.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Paisdor, B

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO,A,96 20009 (MERCK SHARP & DOHME ;HILL RAYMOND GEORGE (GB)) 4 July 1996 see page 100, line 19 - page 104, line 15; claim 1	1-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB96/01478

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 14-18 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/GB 96/01478

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9419323	01-09-94	AU-A-	6109394	14-09-94
		CA-A-	2152925	01-09-94
		EP-A-	0683767	29-11-95
		JP-T-	8506823	23-07-96
EP-A-0577394	05-01-94	AU-A-	4156893	06-01-94
		AU-A-	4656193	24-01-94
		BG-A-	99274	30-04-96
		CA-A-	2099233	30-12-93
		CN-A-	1087902	15-06-94
		CZ-A-	9403330	13-09-95
		FI-A-	946133	28-12-94
		HR-A-	931003	28-02-95
		HU-A-	71809	28-02-96
		JP-A-	6172178	21-06-94
		NO-A-	945064	28-02-95
		NZ-A-	254476	25-09-96
		SI-A-	9300346	31-12-93
		SK-A-	160094	11-07-95
		WO-A-	9400440	06-01-94
		AU-A-	4160893	06-01-94
		ZA-A-	9304624	20-06-94
WO-A-9508549	30-03-95	AU-A-	7697494	10-04-95
		EP-A-	0720609	10-07-96
		FI-A-	961270	03-05-96
		NO-A-	961156	21-05-96
		PL-A-	313619	08-07-96
		ZA-A-	9407291	31-05-95
WO-A-9620009	04-07-96	AU-A-	4185496	19-07-96